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Highlights

- This is the first to examine the longitudinal relationship between four key fitness domains (body composition, muscle endurance, flexibility, and cardiovascular fitness) and future cognitive performance (attention, hand dexterity and working memory) in a sample of inpatients with schizophrenia.
- There is no prospective relationship between each fitness domain and cognitive performance over two years after adjusting for baseline cognitive scores among a cohort of inpatients with established schizophrenia who already had evidence of cognitive dysfunction.

Prospective associations of physical fitness and cognitive performance among inpatients with Schizophrenia

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Abstract

There is a paucity of longitudinal research investigating fitness and cognitive performance in people with schizophrenia. This study examined the prospective associations of physical fitness and cognitive performance among inpatients with schizophrenia. A prospective cohort study over two years was undertaken in 190 inpatients with schizophrenia. Four domains of physical fitness (body composition, muscle endurance, flexibility, and cardiovascular fitness) were measured at baseline in addition to the cognitive domains of attention, hand dexterity and working memory. At baseline, compared to general population normative data, more than one third of the sample had poor cardiovascular fitness, and over half were overweight/obese, had poor muscular fitness and poor flexibility. In the schizophrenia sample, better cardiovascular fitness at baseline was significantly associated with better attention, dexterity, and memory. However, the relationships dissipated after adjusting for baseline cognitive scores. In the final models, aside from baseline cognitive scores, only illness duration was significantly associated with dexterity, and smoking status and duration of hospitilization were associated with working memory. Our data suggest that in a cohort of people with established schizophrenia who already had evidence of cognitive dysfunction, better physical fitness was not associated with improved cognitive performance over two years.

Keywords: exercise, fitness, physical activity, psychiatric disorder, cognition, recovery.

1. Introduction

There is increasing realisation that physical comorbidities (Lawrence et al., 2013), predominantly cardiovascular disease (Correll et al., 2017), are the leading causes of the premature mortality gap of approximately 15 years in people with schizophrenia. Consequently, there has been an increased focus on interventions that can reduce the risk of and manage cardiovascular disease and physical comorbidities in this population (Docherty et al., 2016). There is robust evidence from the general population that physical activity interventions are broadly as effective as common pharmacological interventions in preventing cardiovascular disease mortality (Naci and Ioannidis, 2013). In particular, physical activity interventions that seek to improve fitness have been associated with a number of beneficial outcomes in the general population (Lee et al., 2011) and people with schizophrenia (Vancampfort et al., 2016a). In addition to the physical and mental health benefits of physical activity in schizophrenia (Firth et al., 2015), there is encouraging evidence that this modality may improve cognitive performance (Firth et al., 2016). Poor cognitive performance in schizophrenia is evident in the prodromal phase and is associated with poor functioning and typically deteriorates over the course of the illness (Fusar-Poli et al., 2012; Szoke et al., 2008). There is a pressing need to identify factors that may influence cognition over the course of schizophrenia.

In the general population, there is robust evidence that fitness and its four key domains (body composition, muscle endurance, flexibility, and cardiovascular fitness) are associated with better cognitive performance across the lifespan (Donnelly et al., 2016; Etnier et al., 2003). Little is known about the relationship between fitness and cognitive performance in people with schizophrenia. However, people with schizophrenia have lower levels of muscular fitness, endurance (Vancampfort et al., 2016b) and cardiorespiratory fitness (Vancampfort et al., 2015) compared to the general population. Another large cross sectional study demonstrated that higher muscular function was associated with improvements in multiple cognitive domains in a cohort of over 1000 people with schizophrenia (Firth et al., 2018). Whilst there is some indication of a cross sectional relationship between fitness domains and cognition, there is a paucity of prospective research investigating the longitudinal relationship between fitness and cognitive performance in people with schizophrenia.

Given the aforementioned, we conducted a prospective cohort study to explore the longitudinal relationship between four key components of fitness (body composition, muscle endurance, flexibility, and cardiovascular fitness) with future cognitive performance among inpatients with schizophrenia over 2 years.

2. Methods

2.1 Participants

Participants were recruited from 19 chronic psychiatric wards at Tsaotun Psychiatric Center, Ministry of Health and Welfare, Taiwan. The diagnosis of schizophrenia was verified by psychiatrists based on the Diagnostic and Statistical Manual Disorders, Fifth Edition (DSM-5). Patients were included if they were aged 20-64 years old, were inpatients and were stable on antipsychotic medicine with the same dosage for at least three months prior to inclusion.

Those who were unable to walk independently, unable to communicate or understand instructions, had alcohol or substance abuse, brain injury, or neurological disorders were excluded. These conditions were collected from the hospital records and diagnosed by psychiatric doctors. A total of 240 potential inpatients were suitable for the study and among them, 204 inpatients participated in the study (36 patients were not able to attend the study due to illness or absence). The baseline data were collected in 2015 and the follow-up data for cognitive performance were collected again in 2017. Among the 204 participants, 14 patients discharged, resulting 190 participants for the final analyses. This study was approved by the Institutional Review Board of Tsaotun Psychiatric Center.

2.2 Measures

2.2.1 Physical fitness

This study measured health-related physical fitness, including four components: body composition, flexibility, muscle endurance, and cardiovascular fitness. All of the fitness tests were led and supervised by a certified fitness instructor, who received training. Weight and height were measured and a body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m2), which was used to be the index of body composition. The standardized sit-and-reach test was used to measure the lower back and hip joint flexibility (American College of Sports Medicine, 2003; Vancampfort et al., 2013). The number of bent-knee sit-ups attained in 1 min was used to assess abdominal muscle endurance (Balogun et al., 2017). Participants were encouraged to perform as many bent-knee sit-ups as possible. A higher number of sit-ups indicates a better abdominal muscle endurance. Finally, a 3-min step test was used to test cardiovascular fitness level. Participants stepped on and off a 35 cm high bench with the metronome setting to a rate of 96 beats per minute. A cardiovascular index (CI) was obtained by the following formula: CI= $\frac{\text{Time}\times 100}{(\Sigma\text{pulse})\times 2}$, where Time is the duration of exercise period in seconds and Σpulse is the sum of 3 half-minute pulse counts (1–1$\frac{1}{2}$, 2–2$\frac{1}{2}$, 3–3$\frac{1}{2}$ Min) during recovery (Bosco and Gustafson, 1983; Heyward, 1991). Higher scores indicate better cardiovascular fitness.

Variables of flexibility, muscle endurance, and cardiovascular fitness were each categorized into two groups (‘Fair/Good’ or ‘Poor’) for some analyses based on the age- and sex- specific National Norm for Taiwanese adults aged 20-64 (n=80,218) (Ministry of Education, 2011). Those who had a score ≦ Percentile Rank (PR) 40 in the National Norm were classified as 'Poor' and others were classified as 'Fair/Good (PR 41-60 / PR 61 or over)'. Body composition was also divided into two groups (normal/underweight: body mass index (BMI) <24, overweight/obesity: BMI ≥24) based on the national criteria of obesity in Taiwan.

2.2.2 Cognitive performance

Cognitive performance was tested across the following domains:

Attention: The Chu's Attention Test was used in the study, which is one of the most widely used measures for testing attention in clinical psychiatric settings in Taiwan and showed excellent test-retest reliability among patients with schizophrenia (ICC=0.95) (Lee et al., 2014). The test includes 8 items for practice and 200 items for the formal test, each of which requires the participants to view a series of scrambled codes, look for the "*" sign among the codes, and count the occurrences of "*". The final score is obtained by the total number of correct answers in 10 minutes.

Hand dexterity: The Chu's Hand Dexterity Test was used in this study, which is a test of hand dexterity, hand-eye coordination, and speed of processing. It has been used in previous research among patients with schizophrenia with acceptable test-retest reliability (ICC=0.76-0.87) (Lu et al., 2009). Participants were asked to insert an iron bar into a board in a fixed hole and then, put a nut into the iron bar. They were asked to continue the task in a fixed order and encouraged to perform the task as quickly as possible within 2 minutes using only the right hand, the left hand and the both hands for three times. The total number of iron bars and nuts for each test is recorded and summed, with higher scores indicating better dexterity.

Working memory: The Digit Span subtest from the WISC-IV was used to assess working memory in the study, which has been used previously among patients with schizophrenia (Kolb and Whishaw, 1983). The test consists of two parts: Digit Span Forward and Digit Span Backward. Participants hear a sequence of numerical digits with increasingly longer sequences. The Digit Span Forward requests the participants to repeat the numbers in the same order, while the Digit Span Backward asks the participants to recall the numbers in reverse order. The higher score indicates better performance in this memory test.

All tests were completed by trained occupational therapists.

2.2.3 Covariates

Sociodemographic variables: Details of participants' age, sex, years of schooling, and smoking habits were collected. Information about the current smoking status and alcohol drinking were asked by the occupational therapists and categorized into two groups: 'Yes' and 'No'. Alcohol consumption was not permitted in the hospital, hence no participants consumed alcohol and data were not shown for alcohol consumption.

Clinical related variables: Data on the years since illness onset, duration of hospitalization, the medication use were collected through the hospital records. Antipsychotic medication use was converted into a daily equivalent dosage of chlorpromazine, while anticholinergic drugs were converted into Trihexyphenidyl dose, according to the defined daily dose (DDD) of WHO Collaborating Centre for Drug Statistics Methodology (https://www.whocc.no/atc_ddd_index/).

Metabolic parameters: Data on waist circumference, systolic/diastolic blood pressure (SBP/DBP), serum triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and fasting glucose (FG) were obtained through regular health checks in the hospital. Those who met the following criteria for Asian populations were regarded as abnormal: waist circumference ≥90 cm in men and ≥80 cm in women; SBP/DBP ≥130/85mmhg; serum triglyceride (TG) ≥150 mg/dl; high-density lipoprotein cholesterol (HDL-C) <40 mg/dl in men and <50 mg/dl in women; and fasting glucose (FG) ≥100 mg/dl (Eckel et al., 2005). Then, the number of the abnormal metabolic parameters were counted.

2.3 Statistical analyses

Descriptive statistics were calculated to summarize the participants' characteristics. To examine the independent association between each components of fitness and cognition, multivariable linear regression analyses were conducted. Separate regressions were performed for each of the cognitive tests. The dependent variable was cognitive performance at follow-up in 2017. The four components of fitness (body composition, flexibility, muscle endurance, and cardiovascular fitness) were entered into the first model. The second model was adjusted with sociodemographic variables (age, sex, schooling, and smoking status), MetS status, and clinical characteristics (years since illness onset, duration of hospitalization, and medication use). The final model was further adjusted with baseline cognitive performance in 2015 except variables adjusted in model 2. All analyses were performed with IBM SPSS statistics 22 and a *p*-value less than 0.05 was considered as statistically significant.

3. Results

The final sample included 190 people with schizophrenia with a mean age of 45.11 years. Almost one third of the sample were female (36.32%) and a similar proportion currently smoked (31.58%) (full details of the final sample are displayed in table 1). All of the inpatients were taking antipsychotic medication, with a mean illness duration of 23.64 year, with an average length in hospital of 64.08 months.

Insert table 1 here

The baseline fitness levels of the sample, compared to general population normative data are displayed in table 2. Briefly, 34.21% had poor cardiovascular fitness (≤PR 40), just over half (51.05%) had poor muscular fitness, 61.90% had poor flexibility and 58.95% were overweight/obese.

Table 2 here

Figure 1 and 2 display the changes in attention, dexterity and memory in the whole sample over the two year follow up period, with evidence of a significant deterioration in dexterity ($p<0.001$) and possibly memory ($p=0.002$).

Insert figure 1 and 2 here

The longitudinal relationship between the four domains of fitness and the cognitive parameters are displayed in table 3. In model 1 and 2, cardiovascular fitness was associated with better attention at follow up, however, this relationship was not significant once baseline attention scores were inserted into the final model. Body composition and cardiovascular fitness were associated with dexterity at the two year follow up, but this relationship dissipated after adjusting for baseline dexterity and years of illness remained a significant predictor. Cardiovascular fitness was associated with future memory performance in model 2, although this dissipated in the final model where smoking status, duration of hospitalization and baseline memory score remained the only significant predictors.

Table 3 here

4. Discussion

To the best of our knowledge, the current study is the first to examine the longitudinal relationship between four key fitness domains and future cognitive performance in a sample of inpatients with schizophrenia. In summary, our data suggest that after adjusting for baseline cognitive scores, there is no prospective relationship between each fitness domain and future cognitive performance measures among a cohort of inpatients with established illness.

Previous cross-sectional research suggested that there is a relationship between physical fitness and cognitive performance in people with schizophrenia. For instance, a cross-sectional study with a small sample size (32 patients with schizophrenia) found significant associations between physical fitness and a number of cognitive domains in outpatients (Kimhy et al., 2014). Specifically the authors found that aerobic fitness and BMI displayed significant correlations with some domains of cognitive performance, such as speed of processing, and working memory (Kimhy et al., 2014). In the present study, cardiovascular fitness and body composition (BMI) were also significantly related to several cognitive domains (attention, speed of processing, working memory), whereas this relationship dissipated after adjusting for baseline cognitive scores. Clearly the difference in the samples and study design could account for this contrast. A more recent and large scale study considering 1,162 people with schizophrenia investigated one fitness domain (muscular strength via maximal handgrip strength) and found that greater handgrip strength was strongly related to visual memory (coeff=-0.155, S.E.=0.042, $p<0.001$) and reaction time (coeff=-0.049, S.E.=0.009, $p<0.001$) (Firth et al., 2018). However, the authors found there was not a relationship between maximal handgrip strength and prospective memory, number memory and reasoning (Firth et al., 2018). Thus, taken together, among people with established schizophrenia, the evidence for the relationship between physical fitness domains and cognitive performance is limited and inconsistent.

There are a number of caveats which preclude any definitive answer being given regarding the relationship between physical fitness and future cognition in people with schizophrenia. First, our study included people with on average an established illness duration of 23.64 years. Previous research has demonstrated that cognitive deficits are evident in the prodromal phases (Fusar-Poli et al., 2012) and typically worsens over the duration of the illness, with the most pronounced deterioration in the first few years of the illness (Kahn and Keefe, 2013). Considering this, one reason for our null result could be that the cognitive deficits observed among our sample were extensive and physical fitness may no longer could confer a positive impact on future cognition. A similar notion has been observed in other cognitive disorders such as dementia, where there is robust evidence for the protective effects of physical fitness in mild cognitive impairment/early dementia (Pitkälä et al., 2013; Smith et al., 2014; Wierenga, 2011), yet the protective effects of fitness interventions in more marked cognitive impairment are not evident (Lamb et al., 2018). Our findings and the wider literature on cognition add to further calls to provide early intervention to see if improving physical fitness at the onset of psychotic illness can prevent or delay the onset of the cognitive symptoms (Lamb et al., 2018). Another caveat of our data is that the included participants had on average been in hospital for a considerable length of time (64.08 months). Clearly people who have been in hospital for such a length of time are most unwell in terms of symptoms and often on the highest doses of antipsychotic medication, both of which have been associated with worse cognitive symptoms (Kahn, 2013; Kahn and Keefe, 2013). Whilst we adjusted for antipsychotic medication, this factor could have played an important role. Given this, we cannot assume that our results transfer to people with established illness in the community, who may have less pronounced symptoms and cognition. Future longitudinal research should seek to explore the relationship between fitness and cognitive outcomes in people living in the community. Finally, we only followed up participants for two years and it may be that this was too short a time frame for any changes to occur in cognitive performance in a sample of people with established schizophrenia.

Whilst our data addresses an important gap within the literature, some limitations need to be considered. As illustrated above, our sample only followed up participants for two years. Thus, future longer term follow up is required to better understand the relationship between physical fitness and cognitive performance and schizophrenia. Second, our study only included in patients with established schizophrenia. Our results do not generalize beyond this setting or illness duration and early intervention work to explore the relationship between physical fitness and cognition is needed in people with first episode psychosis. Finally, the sample size of 190 was relatively modest.

In conclusion, our data does not support the protective effects of higher physical fitness on future cognitive ability in people with established schizophrenia spectrum disorders. Future research on younger, first episode people with psychosis may be the more optimal time to investigate the potential protective effect of physical fitness on cognition.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of Interest

The authors declare that they have no conflict of interest.

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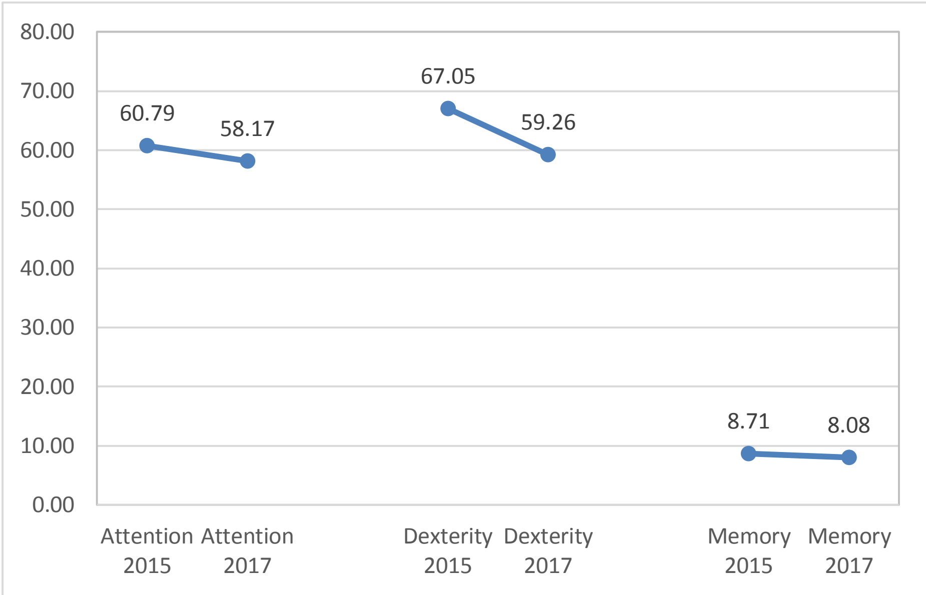
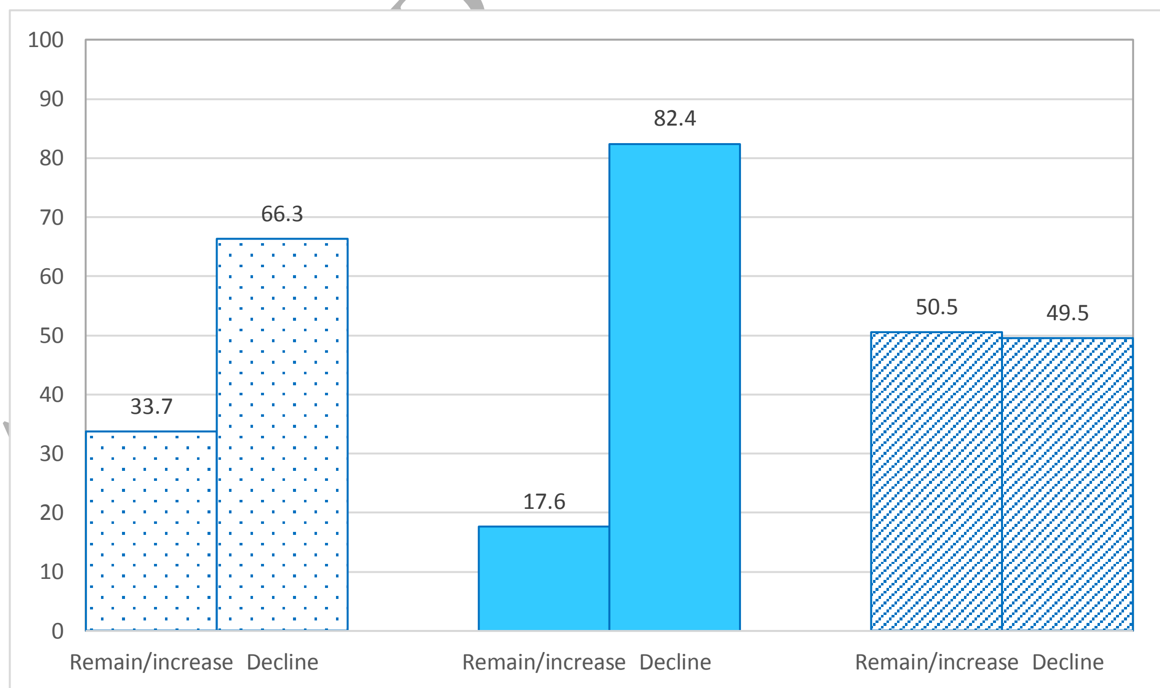


p = .092 p < .001 p = .002

Figure 1: Cognitive performance of participants between 2015 and 2017



% Attention Dexterity Memory

Figure 2: Changes of cognitive function among participants over two years

Table 1: Descriptive statistics of participants at baseline

Variable (n=190)	Mean ± SD or %
Age (years)	45.11 ± 8.78
Sex (%)	
Female	36.32
Male	63.68
Smoking status (%)	
Yes	31.58
No	68.42
Schooling (years)	10.74 ± 2.94
Count of MetS	1.76 ± 1.34
Years since illness onset	23.64 ± 8.57
Duration of hospitalization (month)	64.08 ± 52.59
Medications (mg/d)	
Antipsychotics (Chlorpromazine doses)	807.38 ± 538.19
Anticholinergic (Trihexyphenidyl dose)[a]	18.46 ± 8.12
Cognitive Function	
Attention	60.79 ± 24.52
Dexterity	67.05 ± 18.79
Memory	8.71 ± 3.20
Fitness components (mean)	
Body composition (BMI)	25.18 ± 4.66
Cardiovascular fitness	55.48 ± 15.21
Muscular endurance	21.12 ± 10.99
Flexibility	17.70 ± 10.71

[a]: Mean in those who took the anticholinergic agent (n =39)

Abbreviations: MetS: metabolic syndrome; BMI: body mass index

Table 2: Baseline fitness levels of patients with schizophrenia using the cut-off points of the National Norm with the general population

Fitness components (n=190)	%
Body composition (BMI)	
Overweight/obese (≧24)	58.95
Normal/underweight	41.05
Cardiovascular fitness	
Poor (≤PR 40)	34.21
Fair or good	65.79
Muscular endurance	
Poor (≤PR 40)	51.05
Fair or good	48.95
Flexibility	
Poor (≤PR 40)	61.90
Fair or good	38.10

Abbreviations: PR: Percentile Rank; BMI: body mass index

Table 3: Linear regressions for predicting cognitive performance after two years

Variables	Model 1[a]			Model 2[b]			Model 3[c]		
	R^2	Beta	*P*	R^2	Beta	*p*	R^2	Beta	*p*
Predictor: Attention	0.077			0.167			0.344		
Body composition (BMI)		0.036	0.621		0.071	0.322		0.074	0.250
Muscular endurance		0.094	0.206		0.095	0.197		0.040	0.543
Flexibility		0.100	0.173		0.100	0.167		0.097	0.133
Cardiovascular fitness		0.248	0.001		0.237	0.002		0.016	0.830
Age					0.015	0.892		-0.013	0.895
Sex					0.008	0.928		-0.005	0.947
Smoking status					0.150	0.071		0.107	0.148
Schooling					0.246	0.001		0.093	0.167
Count of MetS					-0.069	0.365		-0.071	0.292
Years since illness onset					-0.072	0.517		-0.060	0.541
Duration of hospitalization					-0.038	0.598		0.002	0.978
Antipsychotics					-0.029	0.694		-0.002	0.978
Anticholinergic					0.026	0.717		0.062	0.344
Baseline attention score								0.502	<0.001
Predictor: Dexterity	0.204			0.288			0.484		
Body composition (BMI)		-0.128	0.059		-0.137	0.042		-0.061	0.292
Muscular endurance		0.061	0.381		0.034	0.615		-0.007	0.904
Flexibility		-0.021	0.756		-0.033	0.625		0.016	0.777
Cardiovascular fitness		0.448	<0.001		0.401	<0.001		0.061	0.402
Age					0.262	0.011		0.172	0.052
Sex					0.027	0.730		0.010	0.883
Smoking status					0.091	0.237		0.084	0.199
Schooling					-0.105	0.110		-0.062	0.268
Count of MetS					0.076	0.281		0.078	0.199
Years since illness onset					-0.360	0.001		-0.219	0.016
Duration of hospitalization					0.015	0.824		-0.022	0.703
Antipsychotics					-0.041	0.554		-0.003	0.963
Anticholinergic					-0.109	0.110		-0.075	0.200
Baseline dexterity score								0.576	<0.001
Predictor: Memory	0.183			0.235			0.354		
Body composition (BMI)		-0.035	0.606		-0.039	0.570		-0.049	0.439
Muscular endurance		0.090	0.197		0.101	0.153		0.090	0.166
Flexibility		0.015	0.829		-0.001	0.993		-0.005	0.934
Cardiovascular fitness		0.436	<0.001		0.437	<0.001		-0.233	0.090
Age					-0.133	0.207		-0.037	0.708
Sex					0.078	0.334		0.034	0.651
Smoking status					0.149	0.062		0.153	0.037
Schooling					0.087	0.202		0.109	0.083
Count of MetS					-0.115	0.114		-0.060	0.380
Years since illness onset					0.163	0.127		0.009	0.933
Duration of hospitalization					0.106	0.130		0.134	0.038
Antipsychotics					0.086	0.230		0.112	0.091
Anticholinergic					0.060	0.391		0.038	0.552
Baseline memory score								0.741	<0.001

[a]: Model 1: only four fitness components were entered into the regression model

[b]: Model 2: Model 1 + nine covariates (demographic variables, health condition, medications)
[c]: Model 3: Model 1 + Model 2 + baseline cognitive performance score